Synthesis of Substances Related to the Sex Hormones

1. Phenanthrene Derivatives. 1-Alkyl-1-hydroxy-tetrahydrophenanthrenes and Related Compounds.
2. The Synthesis of *cis* and *trans* 17-Equilenone.

A DISSERTATION

SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
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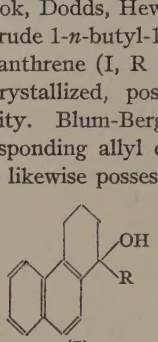
[Contribution from the Chemistry Laboratory of the University of Michigan]

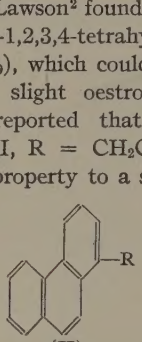
Phenanthrene Derivatives. IX. 1-Alkyl-1-hydroxytetrahydrophenanthrenes and Related Compounds

By W. E. Bachmann and A. L. Wilds[1]

Cook, Dodds, Hewett and Lawson[2] found that the crude 1-*n*-butyl-1-hydroxy-1,2,3,4-tetrahydrophenanthrene (I, R = *n*-C_4H_9), which could not be crystallized, possessed a slight oestrogenic activity. Blum-Bergmann[3] reported that the corresponding allyl carbinol (I, R = $CH_2CH{=}CH_2$) likewise possessed this property to a slight



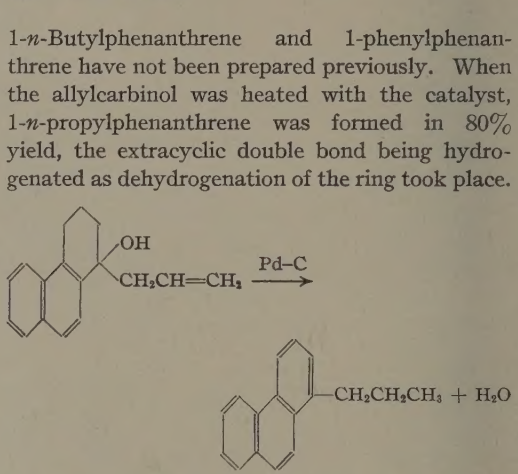
(I)



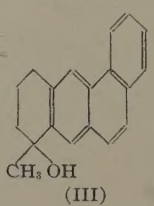
(II)

extent. We have now prepared the methyl, ethyl and *n*-propylcarbinols (I, R = CH_3, C_2H_5, *n*-C_3H_7) in order to determine the effect of these alkyl groups on the oestrogenic activity of the molecule. These compounds were obtained in crystalline form from 1-keto-1,2,3,4-tetrahydrophenanthrene through the Grignard reaction. Although Haworth[4] prepared the same compounds as intermediates in the synthesis of 1-alkylphenanthrenes, apparently he did not obtain the carbinols in a crystalline condition. Solutions of our three carbinols in sesame oil were injected into rats, but no oestrogenic activity was observed even with 100-mg. doses (Dr. Bradbury).

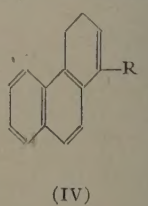
Haworth prepared 1-alkylphenanthrenes by dehydrating the crude carbinols (I) and dehydrogenating the products by reaction with selenium at 300–330° for twenty-four hours. We have obtained the 1-methyl-, 1-ethyl- and 1-*n*-propylphenanthrene (II, R = CH_3, C_2H_5, *n*-C_3H_7) in 90–98% yields by heating the crystalline carbinols with a palladium–charcoal catalyst at 310–320° for one-half hour. Similarly, we prepared 1-isopropylphenanthrene and 1-*n*-butylphenanthrene from the crude non-crystalline carbinols, and have also made 1-phenylphenanthrene from the crystalline 1-phenyl-1-hydroxy-1,2,3,4-tetrahydrophenanthrene (I, R = C_6H_5). 1-*n*-Butylphenanthrene and 1-phenylphenanthrene have not been prepared previously. When the allylcarbinol was heated with the catalyst, 1-*n*-propylphenanthrene was formed in 80% yield, the extracyclic double bond being hydrogenated as dehydrogenation of the ring took place.



This procedure constitutes an excellent method for preparing this hydrocarbon since the allylcarbinol can be obtained from the cyclic ketone in nearly quantitative yield. The catalyst was also used with success to obtain the carcinogenic hydrocarbon 5-methyl-1,2-benzanthracene directly from the crystalline 5-methyl-5-hydroxy-5,6,7,8-tetrahydro-1,2-benzanthracene (III). It



(III)



(IV)

was found that the catalyst which was recovered from one run could be used without loss of its efficacy for the conversion of a second batch of carbinol to 5-methyl-1,2-benzanthracene.

Dehydration of the 1-alkyl-1-hydroxy-1,2,3,4-tetrahydrophenanthrenes by potassium acid sulfate at 160° gave mixtures from which only some 1-alkylphenanthrene could be isolated in small amount, an indication that the dehydration process was accompanied by dehydrogenation. It was found that the hydrocarbons resulting from dehydration usually could be obtained in a pure crystalline form by heating the carbinols in a sublimation apparatus at 180–200° at 0.5 mm.;

(1) From part of the Ph.D. dissertation of A. L. Wilds.

(2) Cook, Dodds, Hewett and Lawson, *Proc. Roy. Soc.* (London), **114B**, 274 (1934).

(3) Blum-Bergmann, *Naturwissenschaften*, **21**, 578 (1933).

(4) Haworth, *J. Chem. Soc.*, 1130 (1932); 460 (1934).

under these conditions the hydrocarbons collected on the cool part of the apparatus in excellent yields. The products of the dehydration are presumably 1-alkyl-3,4-dihydrophenanthrenes (IV), although the isomeric structure with a double bond going to the side chain is not excluded. It is noteworthy that only a single product was obtained on dehydration. As was to be expected, the dihydro compounds were readily converted to the alkylphenanthrenes by the palladium–charcoal catalyst.

Experimental

1-Methyl-1-hydroxy-1,2,3,4-tetrahydrophenanthrene (I, R = CH_3).—To the ice-cold Grignard reagent prepared from 1.5 cc. of methyl iodide and 0.5 g. of magnesium in 20 cc. of ether was added a solution of 2 g. of 1-keto-1,2,3,4-tetrahydrophenanthrene[4] in 10 cc. of benzene; throughout the reaction the mixture was kept at 0°. After the mixture had stood in a refrigerator for twelve hours, a large amount of crystalline addition product was present. These crystals were filtered off and hydrolyzed with ice-cold ammonium chloride solution, and the carbinol was extracted with benzene. On evaporation of the solvent at room temperature in an evaporating dish, the carbinol crystallized; yield 1.4 g. From the original ether–benzene reaction mixture an additional quantity of the carbinol was isolated, bringing the total yield to 84–88% of the calcd. amount. 1-Methyl-1-hydroxy-1,2,3,4-tetrahydrophenanthrene crystallizes from benzene–ligroin in clusters of colorless needles; m. p. 86.0–86.5°. The carbinol gives a rose-red color with concentrated sulfuric acid.

Anal. Calcd. for $C_{15}H_{16}O$: C, 84.9; H, 7.5. Found: C, 84.8; H, 7.5.

1-Methyl-3,4-dihydrophenanthrene.—One-half gram of the aforementioned carbinol was dehydrated by heating it in a sublimation apparatus at 180–200° for fifteen minutes and then subliming at 0.5 mm. By recrystallization of the condensate from dilute alcohol 0.37 g. (80%) of 1-methyl-3,4-dihydrophenanthrene was obtained. The hydrocarbon crystallizes from methanol in colorless plates; m. p. 86.0–86.5°. A mixture of the carbinol and the hydrocarbon melted below 70°.

Anal. Calcd. for $C_{15}H_{14}$: C, 92.8; H, 7.2. Found: C, 92.9; H, 7.3.

When the carbinol was heated with one and one-half times its weight of powdered potassium acid sulfate at 160° for one hour, a crystalline mixture was obtained from which a small amount of 1-methylphenanthrene was isolated. Cook and Hewett[5] mentioned that they isolated the crystalline dihydro derivative, which melted at 82–83°, but they reported no details.

Conversion of the Carbinols to Phenanthrene Compounds.—A mixture of 1 g. of the carbinol and 0.1 g. of 30% palladium–charcoal catalyst prepared according to the procedure of Zelinsky and Turowa-Pollak[6] was heated in a nitrogen atmosphere at 310–320° for one-half hour. A gas buret was employed to measure the amount of hydrogen evolved, and although the volume of gas corresponded only roughly to the calculated amount, it served as a convenient means of observing the progress of dehydrogenation and the end of the reaction. Usually, most of the hydrogen was evolved during the first five minutes of heating. After removing the hydrogen by evacuating the apparatus and filling it with nitrogen, the hydrocarbon was extracted with acetone.

1-Methylphenanthrene.—A 90% yield of this hydrocarbon was obtained from the carbinol by the method just described. Recrystallized from ethanol, the hydrocarbon formed colorless leaflets; m. p. 120–121°. The picrate formed orange-yellow needles from absolute alcohol and melted at 136.0–136.5°. When the 1-methyl-3,4-dihydrophenanthrene was heated with the calculated amount of sulfur at 260° for one hour, a 25% yield of 1-methylphenanthrene was isolated.

1-Ethyl-1-hydroxy-1,2,3,4-tetrahydrophenanthrene.—Using the procedure described for the preparation of the methyl analog this carbinol was isolated in crystalline form in 78–83% yields. Here, too, the reaction mixture deposited a crystalline addition product from which the carbinol was readily obtained pure. The carbinol crystallizes from ligroin in colorless needles; m. p. 57.0–57.5°. A rose-red color is formed when the carbinol is mixed with concentrated sulfuric acid.

Anal. Calcd. for $C_{16}H_{18}O$: C, 84.9; H, 8.0. Found: C, 84.9; H, 8.1.

1-Ethyl-3,4-dihydrophenanthrene, obtained in 75% yield by dehydration of the carbinol in the manner described for the methyl analog, crystallizes from methanol in colorless leaflets; m. p. 42–43°. When potassium acid sulfate was employed for dehydration, partial dehydrogenation took place, for some 1-ethylphenanthrene was found in the mixture.

Anal. Calcd. for $C_{16}H_{16}$: C, 92.3; H, 7.7. Found: C, 92.5; H, 7.7.

1-Ethylphenanthrene.—This hydrocarbon was obtained in 90% yield directly from the carbinol. From ethanol it crystallized in colorless leaflets; m. p. 63.5–64.0°; the orange-yellow needles of the picrate melted at 109.5–110° (Haworth gives 62.5 and 108–109°, respectively). When the dihydro derivative was heated with selenium at 340° for twelve hours a 25% yield of 1-ethylphenanthrene was obtained.

1-*n*-Propyl-1-hydroxy-1,2,3,4-tetrahydrophenanthrene.—The carbinol was prepared from 1-keto-1,2,3,4-tetrahydrophenanthrene and *n*-propylmagnesium bromide; in this reaction no addition product separated from the Grignard mixture. The residue, obtained by hydrolyzing the reaction mixture with ammonium chloride solution and evaporating the ether–benzene solution, crystallized when stirred with a little ethyl acetate; yield 51%. 1-*n*-Propyl-1-hydroxy-1,2,3,4-tetrahydrophenanthrene crystallizes from benzene–ligroin in clusters of colorless needles; m. p. 87.0–87.5°. With concentrated sulfuric acid the carbinol gives a rose-red color.

Anal. Calcd. for $C_{17}H_{20}O$: C, 85.0; H, 8.4. Found: C, 85.0; H, 8.1.

1-*n*-Propylphenanthrene.—A quantitative yield of this hydrocarbon was obtained directly from the carbinol.

(5) Cook and Hewett, *J. Chem. Soc.*, 1105 (1933).
(6) Zelinsky and Turowa-Pollak, *Ber.*, **58**, 1295 (1925).

From ethanol the hydrocarbon crystallized in colorless needles; m. p. 32–33; picrate, m. p. 100–100.5° (Haworth gives 34–35° and 100–101°, respectively).

The identical hydrocarbon was obtained in 80% yield by heating 0.5 g. of 1-allyl-1-hydroxy-1,2,3,4-tetrahydrophenanthrene[7] with 0.05 g. of the palladium–charcoal catalyst at 215–220° for one-half hour. The same yield of 1-*n*-propylphenanthrene was obtained by heating the mixture at 320° for only ten minutes.

1-Isopropyl-3,4-dihydrophenanthrene.—The carbinol formed by the reaction of isopropylmagnesium bromide and the cyclic ketone could not be obtained crystalline. Dehydration of the crude liquid carbinol from 2 g. of 1-keto-1,2,3,4-tetrahydrophenanthrene gave 0.57 g. (25%) of the dihydro compound. The latter crystallizes from dilute ethanol in colorless plates; m. p. 66–67°.

Anal. Calcd. for $C_{17}H_{18}$: C, 91.9; H, 8.1. Found: C, 91.7; H, 8.1.

1-Isopropylphenanthrene.—A 65% yield of this hydrocarbon was isolated from the product obtained by heating the crystalline dihydro derivative with the catalyst at 250° for forty-five minutes. After purification through the picrate (m. p. 125–125.5°) the hydrocarbon crystallized from ethanol in colorless plates; m. p. 88–88.5°. Haworth obtained a 50% yield (based on the ketone) of this hydrocarbon; m. p. 85–86° (picrate, m. p. 125–126°).

1-*n*-Butylphenanthrene.—Like Cook, *et al.*,[2] we were unable to obtain the *n*-butylcarbinol in crystalline form. When the crude product, obtained from 2 g. of 1-keto-1,2,3,4-tetrahydrophenanthrene and *n*-butylmagnesium bromide, was heated with the palladium–charcoal catalyst at 310–320° for one-half hour, 1.41 g. (59%) of 1-*n*-butylphenanthrene was obtained. When the crude carbinol was dehydrated with potassium acid sulfate at 160° for one hour and the product was heated with the calculated amount of sulfur at 260° for one hour, a 56% yield (based on the ketone) of the hydrocarbon was isolated. 1-*n*-Butylphenanthrene crystallizes from ethanol–acetone in colorless needles; m. p. 42°.

Anal. Calcd. for $C_{18}H_{18}$: C, 92.3; H, 7.7. Found: C, 92.0; H, 7.7.

The picrate crystallizes from absolute alcohol in light yellow needles; m. p. 99–99.5°.

Anal. Calcd. for $C_{18}H_{18}\cdot C_6H_3O_7N_3$: N, 9.1. Found: N, 9.1.

1-Phenyl-1-hydroxy-1,2,3,4-tetrahydrophenanthrene.—A solution of 5 g. of 1-keto-1,2,3,4-tetrahydrophenanthrene in 15 cc. of benzene was added to the ice-cold Grignard reagent prepared from 7.8 g. of bromobenzene and 1.25 g. of magnesium in 50 cc. of ether. The carbinol which was obtained by hydrolysis of the mixture after twelve hours crystallized when stirred with a small amount of benzene–ligroin; yield, 5.3 g. (75%). The carbinol crystallizes from benzene–ligroin in square, colorless plates; m. p. 115–115.5°. A greenish-red color is formed when sulfuric acid is placed on the carbinol.

Anal. Calcd. for $C_{20}H_{18}O$: C, 87.6; H, 6.6. Found: C, 87.8; H, 6.7.

1-Phenyl-3,4-dihydrophenanthrene was formed in 95% yield when the carbinol was heated at 180–200° at 0.6 mm. It crystallizes from ethanol in bundles of colorless needles; m. p. 98°.

Anal. Calcd. for $C_{20}H_{16}$: C, 93.7; H, 6.3. Found: C, 93.9; H, 6.2.

1-Phenylphenanthrene, isolated in 94% yield from the reaction between the carbinol and the catalyst, crystallizes from ethanol in clusters of colorless leaflets; m. p. 79–79.5°.

Anal. Calcd. for $C_{20}H_{14}$: C, 94.5; H, 5.5. Found: C, 95.0; H, 5.5.

The picrate crystallizes from absolute alcohol in orange-yellow needles; m. p. 117–117.5°.

Anal. Calcd. for $C_{20}H_{14}\cdot C_6H_3O_7N_3$: N, 8.7. Found: N, 8.8.

5-Methyl-5-hydroxy-5,6,7,8-tetrahydro-1,2-benzanthracene (III).—To the Grignard reagent prepared from 6 cc. of methyl iodide and 2.2 g. of magnesium in 40 cc. of ether was added 25 cc. of benzene and then 15 g. of 5-keto-5,6,7,8-tetrahydro-1,2-benzanthracene[8] in the course of five minutes. Heat was evolved and a clear solution was obtained. A few minutes later a crystalline addition product began to precipitate. After the mixture had been kept cold for a few hours, the precipitate was filtered off and hydrolyzed with ice-cold ammonium chloride solution; the carbinol obtained in this manner crystallized readily. From ligroin containing a few drops of acetone, the carbinol crystallized in colorless needles; yield, 10 g. (63%); m. p. 91–95°. The carbinol is very soluble in methanol, acetone and benzene, but is little soluble in ligroin. With concentrated sulfuric acid it gives an orange-brown color.

Anal. Calcd. for $C_{19}H_{18}O$: C, 87.0; H, 6.9. Found: C, 87.1; H, 6.8.

From the ether–benzene filtrate of the original Grignard mixture an additional quantity of carbinol was isolated, bringing the total yield to 86%. In another run the entire reaction mixture was hydrolyzed as soon as all of the cyclic ketone had gone into solution. When the ligroin–benzene solution of the product, obtained by hydrolysis, was seeded with crystals of the carbinol, an 86% yield of crystalline carbinol was obtained in the first crop.

5-Methyl-7,8-dihydro-1,2-benzanthracene was obtained in 87% yield (1.5 g.) when the carbinol (1.86 g.) was kept at 200–250° for thirty minutes and the product then sublimed at this temperature at 0.6 mm. The hydrocarbon crystallizes from acetone–alcohol in colorless plates; m. p. 118–118.5°.

Anal. Calcd. for $C_{19}H_{16}$: C, 93.4; H, 6.6. Found: C, 93.6; H, 6.4.

5-Methyl-1,2-benzanthracene.—A 78% yield of this hydrocarbon was obtained directly from the carbinol by means of the palladium–charcoal catalyst. The product possessed the properties of 5-methyl-1,2-benzanthracene reported by Cook,[8] who first prepared it by heating the crude carbinol with sulfur. When the carbinol was heated with potassium acid sulfate at 160° for one hour, a crystalline hydrocarbon mixture was obtained (9 g. from 10 g. of carbinol). When 5 g. of this product was heated with

(7) Schlenk and Bergmann, *J. Soc. Chem. Ind.*, **52**, 209t (1933).

(8) Cook, *J. Chem. Soc.*, 1595 (1933); Bachmann and Bradbury, *J. Org. Chem.*, **2**, 179 (1937).

0.5 g. of the catalyst at 310–320° for forty-five minutes, the product distilled (b. p. 272–278° at 3 mm.) from the catalyst and then recrystallized from benzene–alcohol, 4.37 g. (88%) of 5-methyl-1,2-benzanthracene melting at 155–157° was obtained.

Dehydrogenation was also accomplished by heating 0.5 g. of the hydrocarbon mixture obtained by the potassium acid sulfate treatment with 0.07 g. of sulfur at 250° for ten minutes. Copper powder was added to the hot mixture to combine with the excess of sulfur and the product was sublimed under reduced pressure; by recrystallizing the sublimate from benzene–alcohol, 0.35 g. of 5-methyl-1,2-benzanthracene melting at 156.5–157° and 0.05 g. melting at 154–156° was obtained. Cook reports 157.5–158.5° for the melting point of the pure hydrocarbon.

Summary

1-Methyl-, 1-ethyl- and 1-*n*-propyl-1-hydroxy-1,2,3,4-tetrahydrophenanthrene have been obtained in crystalline form and tested for oestrogenic activity. The carbinols can be converted rapidly to 1-alkylphenanthrenes in one operation by means of a palladium–charcoal catalyst. 1-*n*-Butylphenanthrene and 1-phenylphenanthrene have been prepared for the first time. A rapid preparation of 5-methyl-1,2-benzanthracene by means of the catalyst is described.

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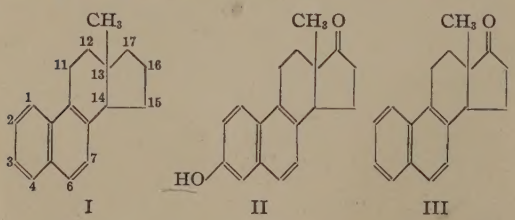
[Contribution from the Chemistry Laboratory of the University of Michigan]

The Synthesis of *cis* and *trans* 17-Equilenone

By W. E. Bachmann and A. L. Wilds[1]

Recently we described the synthesis of *d*- and *l*-equilenin and the diastereoisomers *d*- and *l*-isoequilenin.[2] Of the four optically active stereoisomers, only the *d*-equilenin (the natural hormone) possesses appreciable estrogenic activity. It appeared of interest to determine the effect of removing the hydroxyl group from the molecule. Accordingly, we have synthesized desoxyequilenin and desoxyisoequilenin, both in the racemic forms.

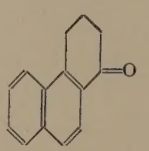
As a matter of convenience in naming the derivatives of equilenin, we propose the following system of nomenclature. The hydrocarbon I is called equilenane, and the sterol system of numbering the positions is retained. The hydrocarbon can exist in *cis* and *trans* forms, each of which is resolvable into optically active isomers, in virtue of the asymmetric carbon atoms at positions 13 and 14. On this basis the sex hormone equilenin (II) is either *cis* or *trans* *d*-3-hydroxy-17-equilenone, the exact configuration not being known definitely. The desoxy compound III is called 17-equilenone and can exist in the four forms: *cis* *d*- and *l*-equilenone and *trans* *d*- and *l*-equilenone. This system of nomenclature will be particularly useful in naming homologs of equilenin and isoequilenin and also isomers of equilenin in which the hydroxyl group has been shifted to various positions in the molecule, compounds which have been synthesized already in this Laboratory.



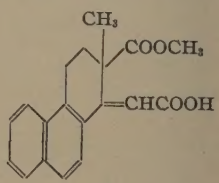
I II III

Although we have synthesized the *cis* and *trans* forms of 17-equilenone, nothing definite is known concerning their configurations or even their relation to equilenin and isoequilenin. Until such information is forthcoming, the compounds are called α-17-equilenone and β-17-equilenone, it being understood that one of them is *cis-dl*-17-equilenone and the other *trans-dl*-17-equilenone. If one can assume that the hydrocarbon obtained by Marker and Rohrmann[3] from natural sources is the equilenane corresponding to equilenin and not to the diastereoisomer, then it should be possible to determine which of the forms of 17-equilenone is related to the natural hormone by resolution of the racemic mixtures and reduction of the optically active forms to the hydrocarbons. This is now under investigation.

The synthesis of the 17-equilenones was accomplished by the same series of reactions which was employed to prepare equilenin and isoequilenin, the starting material in the present synthesis being the readily available 1-keto-1,2,3,4-tetrahydrophenanthrene (IV). Inasmuch as the formulas of the intermediates are identical in the two series, except for a methoxyl group, the formulas are not reproduced in this paper. One point seems worthy of further mention. On dehydration of the hydroxy ester, produced through the Reformatsky reaction from 2-methyl-2-carbomethoxy-1-keto-1,2,3,4-tetrahydrophenanthrene and methyl bromoacetate, a mixture of two unsaturated acids (corresponding to the dicarboxylic acid of V) is formed, one of them readily forming an anhydride. On reduction each unsaturated acid gives a mixture of the same two reduced acids. This fact is considered proof that in the process of dehydration no migration of the methyl group from the 2- to the 1-position takes place. Complete confirmation of the structure of the unsaturated acids was obtained by oxidizing the mono methyl ester (V) of one of them to 2-methyl-2-carbomethoxy-1-keto-1,2,3,4-tetrahydrophenanthrene. A similar result was



IV



V

(1) From part of the Ph.D. dissertation of A. L. Wilds.

(2) Bachmann, Cole and Wilds, This Journal, **62**, 824 (1940).

(3) Marker and Rohrmann, *ibid.*, **61**, 3314 (1939).

obtained with the 7-methoxy unsaturated acid which is an intermediate in the synthesis of equilenin. In view of these results, there can be no doubt concerning the structures of the steroids which have been synthesized.

The racemic *cis* and *trans* forms of 17-equilenone failed to induce estrus in ovariectomized rats when injected in amounts as high as 500 γ (Dr. J. T. Bradbury). This precludes any one optically active form from being active in doses less than 250 γ, provided that the activity of one antipode is not affected by the presence of the other. Since one of the forms present in the racemic mixtures possesses the configuration of *d*-equilenin, which is active in 30 γ doses under the same conditions of testing, it is apparent that removal of the 3-hydroxyl group from the equilenin molecule has resulted in loss of estrogenic activity. This result, taken in conjunction with the lack of activity of the stereoisomers of equilenin, demonstrates the importance of the hydroxyl group as well as the configuration for estrogenic activity of the equilenin molecule.

Experimental

Methyl 1 - Keto - 1,2,3,4 - tetrahydrophenanthrene - 2-glyoxalate.—Certain improvements were made in the preparation of 1-ketotetrahydrophenanthrene whereby the compound was obtained in higher yields than have been reported previously. Twenty cc. of absolute alcohol was added to a mixture of 5.6 g. of sodium and 20 cc. of benzene. When the vigorous reaction had subsided, 50 cc. of diethyl malonate was added and the mixture was refluxed until a clear solution was obtained. To the chilled solution was added 38.5 g. of β-(1-naphthyl)-ethyl bromide[4] in 50 cc. of benzene and the mixture was refluxed for twelve hours, after which it was worked up in the usual manner. The γ-(1-naphthyl)-butyric acid obtained by decarboxylation of the substituted malonic acid was purified by distillation under reduced pressure followed by recrystallization from benzene–petroleum ether; m. p. 109–110°; yield, 33 g. (94%). A sample purified by sublimation under reduced pressure and recrystallization melted at 110.5–112°, a value higher than any that has been reported.

A mixture of 13 g. of the aforementioned acid, 25 cc. of ether, 2 drops of pyridine and 8 cc. of thionyl chloride was allowed to stand at room temperature for one-half hour and then warmed for ten minutes. The ether and excess of thionyl chloride were removed under reduced pressure, a few cc. of benzene was added and the solvent again removed under reduced pressure, finally at 1 mm. in order to remove traces of thionyl chloride. A solution of the acid chloride in 60 cc. of benzene was cooled in ice and water until partial solidification took place, when a solution of 15 cc. of stannic chloride in 15 cc. of benzene was added. After being swirled for five minutes at 5°, the mixture was hydrolyzed with ice and 50 cc. of concentrated hydrochloric acid; a little ether was added in order to break up the emulsion which formed. The 1-ketotetrahydrophenanthrene was distilled under reduced pressure and then recrystallized from methanol; m. p. 94–96°; yield, 11.0–11.2 g. (92–94%). Haworth[5] obtained this ketone in 70–75% yield by cyclizing the acid by means of 85% sulfuric acid, and Hoch[4] obtained a 70% yield by interaction of the free acid and stannic chloride.

The glyoxalate was obtained in 95% yield from 1-ketotetrahydrophenanthrene (19.6 g.), methyl oxalate (23.6 g.) and sodium methoxide (from 4.6 g. of sodium) in benzene (150 cc.) in a nitrogen atmosphere according to the procedure described for the corresponding 7-methoxy derivative.[2] An 85% yield was obtained when the condensation was carried out in air. The glyoxalate (26.9 g.) crystallized from methanol in light-yellow prisms; m. p. 106–108°. The solid formed on cooling the melt remelted at 90–91°; seeding at 95° caused the melt to solidify slowly, the solid remelting at 106–108°. A red-brown color is formed when the glyoxalate is treated with an alcoholic solution of ferric chloride or with concentrated sulfuric acid.

Anal. Calcd. for $C_{17}H_{14}O_4$: C, 72.3; H, 5.0. Found: C, 72.3; H, 5.1.

Methyl Ester of 1-Keto-1,2,3,4-tetrahydro-2-phenanthroic Acid.—Ten grams of the glyoxalate and 5 g. of powdered soft glass were heated at 180–200° for forty-five minutes with occasional stirring. Frequently the glyoxalate could be decarbonylated without the use of glass. A solution of the product in acetone was treated with Norit, filtered, concentrated and treated with methanol. The total yield of product melting at 85–90° was 8.1–8.4 g. (90–93%). At times the crude product melted at 70–90°, but this also gave excellent results in the next step. A sample of the compound sublimed at 0.5 mm. and then recrystallized from methanol formed colorless plates or needles melting at 88–90° with previous softening. Alcoholic ferric chloride slowly gives a deep blue-green color with the pure ester, while concentrated sulfuric acid gives a light orange color.

Anal. Calcd. for $C_{16}H_{14}O_3$: C, 75.6; H, 5.5. Found: C, 75.7; H, 5.4.

2 - Methyl - 2 - carbomethoxy - 1 - keto - 1,2,3,4 - tetrahydrophenanthrene.—To a solution of sodium methoxide prepared from 10 g. of sodium and 150 cc. of methanol was added 25.4 g. of the aforementioned keto ester and 90 cc. of benzene. After being refluxed for thirty minutes, the mixture was chilled, treated with 15 cc. of methyl iodide and allowed to stand at room temperature for forty-five minutes. A second 15-cc. portion of methyl iodide was added, the mixture allowed to stand at room temperature for thirty minutes and then refluxed for the same length of time. The product, isolated in the usual manner, crystallized from methanol in colorless prisms; m. p. 79–80.5°; yield, 25.3 g. (94%). A sample purified by sublimation and recrystallization melted at 79.5–80.5°. The compound gave no color with alcoholic ferric chloride solution; with concentrated sulfuric acid a light orange color was produced.

Anal. Calcd. for $C_{17}H_{16}O_3$: C, 76.1; H 6.0. Found: C, 76.0; H, 6.0.

(4) Hoch, *Bull. soc. chim.*, [5] **5**, 264 (1938).

(5) Haworth, *J. Chem. Soc.*, 1130 (1932).

When the compound was warmed with 40% potassium hydroxide solution a good yield of 1-keto-2-methyl-1,2,3,4-tetrahydrophenanthrene was obtained.

Dimethyl Ester of 1-Hydroxy-2-methyl-2-carboxy-1,2,3,4-tetrahydrophenanthrene-1-acetic Acid.—The Reformatsky reaction using the aforementioned methyl keto ester was carried out in the manner described.[2] A colorless crystalline addition compound was formed in the reaction. From 2 g. of methyl keto ester 2.32 g. (91%) of the Reformatsky ester was formed which melted at 127–131°. On a 13.4-g. run, the first crop of product weighed 14.5 g. (85%); by re-treating the oil in the mother liquor with zinc and methyl bromoacetate the yield was raised to 93%. The hydroxy ester crystallized from acetone–methanol in colorless prisms melting at 131–133°. When a few crystals were dropped into sulfuric acid, they acquired a transient blue color, changing to green, and finally an orange solution resulted.

Anal. Calcd. for $C_{20}H_{22}O_5$: C, 70.2; H, 6.4. Found: C, 69.9; H, 6.2.

Warming 0.1 g. of the hydroxy ester with 40% potassium hydroxide gave 0.04 g. of 1-keto-2-methyl-1,2,3,4-tetrahydrophenanthrene.

Dehydration of the Reformatsky Ester.—This process was carried out in the manner described.[2] The mixture of *anti* unsaturated acid and *syn* unsaturated acid anhydride (0.52 g.) from 0.68 g. of hydroxy ester was dissolved in hot acetone, boiled with Norit, filtered and evaporated to a small volume; on adding alcohol and cooling there crystallized 0.07 g. of cream-colored, heavy needles of the **anhydride of *syn*-2-methyl-2-carboxy-1,2,3,4-tetrahydrophenanthrylidene-1-acetic acid**; m. p. 188.5–189.5°.

Anal. Calcd. for $C_{18}H_{14}O_3$: C, 77.7; H, 5.0. Found: C, 77.6; H, 4.8.

Dilution of the acetone–alcohol filtrate with water precipitated a solid which on recrystallization from benzene–ligroin yielded 0.33 g. of the *anti* **2-methyl-2-carboxy-1,2,3,4-tetrahydrophenanthrylidene-1-acetic acid.** The pure acid crystallized in colorless square plates melting at 220–221°.

Anal. Calcd. for $C_{18}H_{16}O_4$: C, 73.0; H, 5.4. Found: C, 72.8; H, 5.3.

From the filtrate an additional 0.04 g. of the anhydride was isolated.

The **dimethyl ester** of the *anti* unsaturated acid, prepared by means of diazomethane, crystallized from methanol in colorless plates; m. p. 110–111°.

Anal. Calcd. for $C_{20}H_{20}O_4$: C, 74.1; H, 6.2. Found: C, 74.1; H, 5.9.

Oxidation of the Unsaturated Acid.—For the oxidation we used the monomethyl ester (V) of the *anti* unsaturated acid in the form of its water soluble sodium salt; as the neutral ketone was formed on oxidation it was extracted by benzene and thus escaped the further action of the oxidizing agent. The monomethyl ester was prepared by refluxing a mixture of 1.25 g. of the dimethyl ester of the *anti*-unsaturated acid, 4.3 cc. of *N* sodium hydroxide and 20 cc. of methanol for two hours After two recrystallizations from methanol the monomethyl ester (1.17 g.) formed colorless prisms which melted at 197–199°. A solution of 0.31 g. of the compound in 30 cc. of water containing 1.5 cc. of *N* sodium hydroxide was covered with 10 cc. of benzene. A few drops of a solution of 0.31 g. of potassium permanganate in 50 cc. of water were added, and when the color had disappeared (warming if necessary) the solution was cooled to 0° and the remaining permanganate solution was added in portions during fifteen minutes, allowing each portion to decolorize before more was added. After three hours at 0°, the mixture was diluted and made acid to congo red. Some ether was added to the mixture, the organic layer was separated, washed with water and sodium bicarbonate solution and evaporated. Sublimation of the residue at 180–200° at 0.4 mm. followed by recrystallization yielded 0.15 g. of 2-methyl-2-carbomethoxy-1-keto-1,2,3,4-tetrahydrophenanthrene. The oxidation of the 7-methoxy derivative was carried out in a similar manner.

***cis* and *trans* 2-Methyl-2-carboxy-1,2,3,4-tetrahydrophenanthrene-1-acetic Acid.**—A warm aqueous solution of the potassium salt from 0.3 g. of the *anti* unsaturated acid was shaken with 10 g. of 2% sodium amalgam for fifteen minutes. The reduced acids were dried and dissolved in a mixture of 1.2 cc. of acetic acid and 1.8 cc. of xylene by heating. On cooling, 0.20 g. of **α-2-methyl-2-carboxy-1,2,3,4-tetrahydrophenanthrene-1-acetic acid** crystallized in colorless needles. After a recrystallization from benzene–acetic acid the acid melted at 228–229°. It can be sublimed at 240° under reduced pressure without decomposition. In contrast to the unsaturated acid, it gave no color with concentrated sulfuric acid.

Anal. Calcd. for $C_{18}H_{18}O_4$: C, 72.5; H, 6.0. Found: C, 72.6; H, 6.5.

The **dimethyl ester** of this acid, prepared in 95% yield by means of diazomethane, crystallized from methanol–acetone in colorless prisms; m. p. 106–107°.

Anal. Calcd. for $C_{20}H_{22}O_4$: C, 73.7; H, 6.7. Found: C, 73.3; H, 6.5.

The xylene–acetic acid filtrate from the α-acid was evaporated and the residue crystallized from benzene; in this manner 0.08 g. of the β-acid was obtained; m. p. 160–165° with gas evolution (solvent). A sample of the acid was prepared in a pure condition, free from solvent of crystallization, by hydrolysis of its pure monomethyl ester (preparation given below); from dilute acetic acid the **β-2-methyl-2-carboxy-1,2,3,4-tetrahydrophenanthrene-1-acetic acid** crystallized in clusters of colorless plates; m. p. 182–183°.

Anal. Calcd. for $C_{18}H_{18}O_4$: C, 72.5; H, 6.0. Found: C, 72.4; H, 6.2.

The dimethyl ester of the β-acid was not obtained crystalline. For this reason the isomeric acids may also be separated readily through their dimethyl esters.

Reduction of the salt obtained from the anhydride of *syn* unsaturated acid gave the same reduced acids in essentially the same proportions. In view of this result we usually reduced the mixture of the salts of the unsaturated acids as they were obtained in the dehydration reaction of the Reformatsky ester, without isolation of the free unsaturated acids. This was carried out on 5 to 6 g. quantities of Reformatsky ester as was done with the 7-methoxy derivative.[2]

α-2-Methyl-2-carbomethoxy-1,2,3,4-tetrahydrophenanthrene-1-acetic Acid.—A mixture of 3.26 g. of the

dimethyl ester (m. p. 106°) of the α-acid, 10.5 cc. of *N* sodium hydroxide and 50 cc. of methanol was refluxed for two hours. After removal of the methanol, the residue was dissolved in water. On acidification of the solution the acid ester precipitated in crystalline form, which was suitable for the next step. The acid can be recrystallized by dissolving it in aqueous acetone and allowing the acetone to evaporate slowly. In this manner the compound was obtained in stout, gleaming, colorless needles; m. p. 133–134°; yield, practically quantitative.

Anal. Calcd. for $C_{19}H_{20}O_4$: C, 73.1; H, 6.4. Found: C, 72.5; H, 6.2.

Arndt–Eistert Reaction on the α-Acid Ester.—The reaction was carried out in the manner described for the 7-methoxy derivative.[2] From 1.56 g. of the acid ester 1.53 g. (90%) of the **dimethyl ester of α-2-methyl-2-carboxy-1,2,3,4-tetrahydrophenanthrene-1-propionic acid** (m. p. 92–97°) was obtained which was sufficiently pure for cyclization. A sample purified by sublimation under reduced pressure crystallized from methanol in colorless cubes; m. p. 98–99°.

Anal. Calcd. for $C_{21}H_{24}O_4$: C, 74.1; H, 7.1. Found: C, 73.9; H, 7.0.

The free dicarboxylic acid obtained by hydrolysis of the ester by a concentrated solution of potassium hydroxide in methanol crystallized from xylene–acetic acid in broad, colorless needles; m. p. 213–213.5°.

Anal. Calcd. for $C_{19}H_{20}O_4$: C, 73.1; H, 6.4. Found: C, 72.8; H, 6.5.

α-*dl*-16-Carbomethoxy-17-equilenone.—The cyclization of the aforementioned dimethyl ester was accomplished by means of sodium methoxide in benzene in an atmosphere of nitrogen in the manner described.[2] From 0.2 g. of the dimethyl ester of the substituted propionic acid 0.16 g. (88%) of the cyclized product was obtained in crystalline form. A sample after sublimation at 200° at 0.4 mm. crystallized from methanol–acetone in colorless needle-like prisms; m. p. 124–125°. It gave a bluish-purple color with an alcoholic ferric chloride solution.

Anal. Calcd. for $C_{20}H_{20}O_3$: C, 77.9; H, 6.5. Found: C, 77.8; H, 6.5.

α-*dl*-17-Equilenone.—A suspension of 0.6 g. of α-*dl*-16-carbomethoxy-17-equilenone in 15 cc. of acetic acid, 6 cc. of concentrated hydrochloric acid and 1.2 cc. of water was refluxed in an atmosphere of nitrogen for one hour. The solution was boiled with charcoal, filtered and evaporated to dryness under reduced pressure. A benzene solution of the residue was shaken with sodium bicarbonate solution, the benzene was evaporated, the residue dissolved in alcohol, the solution heated with charcoal, filtered, and concentrated. From the solution a total of 0.46 g. (94%) of the α-*dl*-17-equilenone was obtained in the form of colorless plates. The purest sample, obtained by sublimation under reduced pressure and crystallization from methanol–acetone, melted at 100–101°.

Anal. Calcd. for $C_{18}H_{18}O$: C, 86.4; H, 7.2. Found: C, 86.1; H, 7.2.

The same ketone was obtained, although in poorer yields, by heating the free dicarboxylic acid with acetic anhydride and subliming the residue under reduced pressure. Pyrolysis of the lead salt likewise yielded the cyclic ketone.

The **picrate** of α-*dl*-17-equilenone crystallized from alcohol in fine, yellow needles; m. p. 109.5–110.5°.

Anal. Calcd. for $C_{18}H_{18}O \cdot C_6H_3O_7N_3$: N, 8.77. Found: N, 8.76.

A portion of the cyclic ketone was converted to 1,2-cyclopentenophenanthrene by reduction and dehydrogenation. A mixture of 0.175 g. of the ketone and 10 g. of amalgamated zinc in 2.5 cc. of water, 15 cc. of concentrated hydrochloric acid, 2.5 cc. of acetic acid and 1 cc. of toluene was refluxed for twenty-four hours. The product was sublimed under reduced pressure and then heated with 0.1 g. of palladium–charcoal catalyst at 330° for one and one-half hours. The product obtained by extraction with acetone was sublimed and then recrystallized from alcohol and from acetic acid, yielding 15 mg. of pure 1,2-cyclopentenophenanthrene.

β - 2 - Methyl - 2 - carbomethoxy - 1,2,3,4 - tetrahydrophenanthrene-1-acetic Acid.—The crude β-acid (m. p. 160–165°) (1.6 g.) was treated with diazomethane in ether. The dimethyl ester, which did not crystallize, was converted to the acid ester by partial hydrolysis exactly as described for the isomer. The acid ester crystallized from ether in large, stout, colorless needles; m. p. 155–157.5°; yield, 1.0 g. Recrystallization of a sample from acetone raised the melting point to 156–158°.

Anal. Calcd. for $C_{19}H_{20}O_4$: C, 73.1; H, 6.4. Found: C, 73.0; H, 6.4.

β-*dl*-17-Equilenone.—The Arndt–Eistert reaction was carried out on 1.2 g. of the aforementioned acid ester. The product after sublimation at 200° at 0.5 mm. was an oil which did not crystallize. It was cyclized by one hour of heating with sodium methoxide (from 0.125 g. of sodium) in benzene (10 cc.) in an atmosphere of nitrogen. The **β-*dl*-16-carbomethoxy-17-equilenone** crystallized from methanol in colorless plates (0.75 g.). When it was dissolved in hot acetone, the solution concentrated and treated with methanol, fine thread-like crystals and a few plates crystallized. When the mixture was warmed, the fine crystals dissolved and on cooling the solution only stout colorless plates precipitated; m. p. 131.5–133.5° (vac.). A sample recrystallized repeatedly melted at 134–134.5° (vac.). The compound gives a blue color with alcoholic ferric chloride.

Anal. Calcd. for $C_{20}H_{20}O_3$: C, 77.9; H, 6.5. Found: C, 78.0; H, 6.5.

A mixture of 0.44 g. of the β-*dl*-16-carbomethoxy-17-equilenone, 12 cc. of acetic acid, 4 cc. of concentrated hydrochloric acid and 1 cc. of water was refluxed in an atmosphere of nitrogen for one hour. On being cooled, the solution deposited the **β-*dl*-17-equilenone** in practically quantitative yield. After sublimation under reduced pressure it crystallized from acetone–alcohol in colorless plates; m. p. 188.5–189.5° (vac.). It failed to form a crystalline picrate in alcohol and in benzene solution.

Anal. Calcd. for $C_{18}H_{18}O$: C, 86.4; H, 7.2. Found: C, 86.3; H, 7.2.

Summary

The synthesis of the *cis* and *trans* forms of 17-

equilenone (desoxyequilenin and desoxyisoequilenin) is described.

Neither compound has shown estrogenic activity when injected into ovariectomized rats in amounts up to 500 γ.

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